



## Summary of Antihypertensives Sympatholytics

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September 2013

The literature review is current through March 2, 2017.

### FDA-APPROVED INDICATIONS AND DOSAGES<sup>1</sup>

Drug	Manufacturer	Indication(s)	Initial Dosage	Maintenance and Maximum Daily Dose	Availability
clonidine immediate-release tablet (Catapres®) <sup>2</sup>	generic	Hypertension	0.1 mg twice daily (morning and bedtime)	0.2 mg to 0.6 mg daily in divided doses; Maximum daily dose is 2.4 mg	0.1 mg , 0.2 mg, and 0.3 mg immediate-release tablets
clonidine transdermal (Catapres-TTS®) <sup>3</sup>	generic	Hypertension	Apply one 0.1 mg/24 hr transdermal patch every seven days to a hairless area of intact skin on the upper outer arm or chest	If the desired blood pressure reduction does not occur within the first two weeks, an additional TTS-1 patch may be applied or a larger system may be used. More than two of the TTS-3 transdermal patches have not been associated with increased efficacy.	0.1 mg/24 hr transdermal 0.2 mg/24 hr transdermal 0.3 mg/24 hr transdermal

**FDA-Approved Indications and Dosages (continued)**

Drug	Manufacturer	Indication(s)	Initial Dosage	Maintenance and Maximum Daily Dose	Availability
clonidine /chlorthalidone (Clorpres®)	Mylan	Hypertension	1 or 2 tablets two to four times daily	Maximum recommended daily dose of 2.4 mg of clonidine; titrate dose in increments of 0.1 mg to 0.2 mg of clonidine daily until the desired response is achieved.	0.1 mg/15 mg tablet 0.2 mg/15 mg tablet 0.3 mg/15 mg tablet
guanfacine (Tenex®) <sup>4</sup>	generic	Hypertension	1 mg once daily at bedtime	Maximum dose is 3 mg to 4 mg daily. Increase dose after first three to four weeks to 2 mg once daily then further increases up to 3 mg once daily if needed.	1 mg, 2 mg tablet
methyldopa	generic	Hypertension Hypertensive emergency Hypertensive urgency	Adults: 250 mg two to three times daily Pediatrics: 10 mg per kg per day in two to four divided doses Neonates: 5 mg to 10 mg per kg daily in divided doses every six to eight hours	500 mg to 2000 mg daily in two to four divided doses. Maximum adult dose is 3,000 mg daily. Maximum geriatric dose is 1,000 mg daily. Maximum pediatric daily dose is 65 mg per kg per day or 3,000 mg daily, or whichever is less	250 mg, 500 mg tablets

***FDA-Approved Indications and Dosages (continued)***

Drug	Manufacturer	Indication(s)	Initial Dosage	Maintenance and Maximum Daily Dose	Availability
methyldopa/ hydrochlorothiazide	generic	Hypertension	One 250 mg/15 mg tablet two or three times daily or one 250 mg/25 mg tablet twice daily or one 500 mg/30 mg or 500 mg/50 mg tablet once daily	Maximum recommended dose of methyldopa component is 750 mg daily and of HCTZ component is 50 mg daily	250 mg/15 mg tablet 250 mg/25 mg tablet
reserpine	generic	Hypertension	0.05 mg to 0.1 mg once daily	0.1 mg to 0.25 mg once daily as maintenance dose Maximum adult daily dose is 0.5 mg and maximum geriatric daily dose is 0.25 mg	0.1 mg, 0.25 mg tablets

## OVERVIEW

Hypertension (HTN) affects approximately 34 percent of adult Americans and is an independent risk factor for the development of cardiovascular (CV) disease.<sup>5</sup> To reduce the risk of CV events, the current blood pressure goal is less than 140/90 mm Hg for most patients. For patients with diabetes the current blood pressure goal is less than 140/80 mmHg, although lower targets may be appropriate in some patients.<sup>6</sup> The blood pressure goal is less than 130/80 mm Hg in for patients with chronic renal disease, with or without diabetes.<sup>7</sup>

Severe HTN (systolic blood pressure  $\geq 180$  and/or diastolic blood pressure  $\geq 120$  mg Hg) can produce acute life-threatening complications and considered hypertensive emergencies. Patients with such high HTN who are asymptomatic and do not display acute end organ damage are considered hypertensive urgencies.

Clonidine and guanfacine (centrally-acting  $\alpha_2$  adrenergic agonists); methyldopa (dihydroxyphenylalanine [DOPA] carboxylase inhibitor; and reserpine (catecholamine reuptake inhibitor) are the focus of this sympatholytic review.

## SPECIAL USAGE CONSIDERATIONS<sup>8</sup>

Abrupt discontinuation of clonidine, regardless of the route of administration, can precipitate a withdrawal syndrome consisting of rebound increases in both serum and urine catecholamines; therefore taper slowly to avoid withdrawal syndrome. Rebound HTN has also been reported with methyldopa and guanfacine.

Methyldopa is contraindicated for use with monoamine oxidase inhibitors (MAOIs), active hepatic disease, such as acute hepatitis and decompensated cirrhosis. Because of the risk of hemolytic anemia, patients receiving methyldopa should have a baseline hemoglobin, hematocrit, or red blood cell count assessed before and during therapy. Positive Coombs' tests occur in ten to 20 percent of patients receiving methyldopa therapy within six to 12 months of therapy, with the lowest incidence occurring with a daily dosage of one gram or less.

Reserpine is contraindicated in patients receiving electroconvulsive therapy (ECT), active peptic ulcer disease or ulcerative colitis, in patients with a history of major depression.

Avoid tricyclic antidepressants (TCAs) with clonidine and reserpine.

Methyldopa oral dosage forms and guanfacine are classified as Pregnancy Category B. Methyldopa/HCTZ, clonidine, and reserpine are Pregnancy Category C. Methyldopa has been used in pregnancy with long-term fetal safety, but it causes sedation.<sup>9</sup>

Dosage changes may need to be made for each agent based on other concomitant medications decreased renal and/or hepatic function, and tolerability of the agent.

## PLACE IN THERAPY<sup>10,11,12,13</sup>

The Eighth Joint National Committee Guidelines on the Management of High Blood Pressure in Adults (JNC-8) recommends either a thiazide diuretic, angiotensin converting enzyme (ACE) inhibitor, calcium channel blocker (CCB), or angiotensin II receptor blocker (ARB) for first-line therapy for most hypertensive patients.<sup>14</sup> Comparative data was limited with centrally-acting alpha2 adrenergic agonists, methyldopa, and reserpine during the review of the literature for JNC-8; none of these agents are considered first line for the treatment of hypertension. Despite lacking a first-line treatment recommendation and several other classes of antihypertensives to choose from, the sympatholytics remain a treatment option for hypertension for patients refractory or sensitive to the newer agents.

The oral, centrally-acting, alpha2-adrenergic receptor agonists currently in use include clonidine and guanfacine. Clonidine (Catapres) is available in both a transdermal formulation and an oral formulation for the treatment of hypertension. Clonidine and chlorthalidone (Clorpres) are also generically available in a combination tablet formulation. Guanfacine (Tenex) is used alone or in combination with other drugs for the treatment of hypertension. While it is similar to clonidine, guanfacine is more selective for alpha2-adrenergic receptors, longer acting, dosed once daily, and has less frequency and severity of rebound hypertension following abrupt discontinuation. Methyldopa is a centrally-acting antihypertensive agent, which was commonly used in the past for blood pressure control but whose use has largely been replaced by other antihypertensive drug classes with more favorable adverse effect profiles. However, methyldopa is still used in developing countries due to its low cost and in the treatment of chronic hypertension in pregnant women. However, a meta-analysis of methyldopa for the treatment of hypertension in pregnant females found no difference on the risk of pre-eclampsia, fetal demise, preterm birth, or small for gestational age babies despite blood pressure reduction.<sup>15</sup> Hydrochlorothiazide and methyldopa are used together in an oral preparation for the treatment of hypertension. The effects are additive for blood pressure reduction with the combination of hydrochlorothiazide and methyldopa. The combination product may be used once the dose has been successfully titrated and the optimal dose corresponds to a ratio contained in the combination formulation. The use, however, of this combination product should be minimal due to dosing constraints from each individual component found in the combination product. The HCTZ component negates the use of this combination product in pregnant women. Reserpine has been used as a second-line therapy. Recently, the use of reserpine as an antihypertensive agent has diminished due its adverse CNS effects. Newer agents have shown to be much better tolerated.

In the absence of compelling indications, reaching target blood pressure is central in determining cardiovascular benefit in patients with hypertension, not the specific agent used to reach target blood pressure.<sup>16,17</sup> In hypertensive patients with lower BP goals or with substantially elevated BP, three or more antihypertensive drugs may be necessary.

There are no comparative clinical trials evaluating the sympatholytic antihypertensives. Good quality, double-blind, comparative trials have not been performed with these agents in the management of hypertension.

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